

Multidisciplinary Symposium — Prostate Cancer

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Planning primary therapy

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Currently, urological surgeons influenced by the predominance of American urologists in this field have little or no place for the use of imaging modalities in determining whether a patient is suitable for radical prostatectomy with curative intent. They have endeavoured by combining clinical parameters to identify low, intermediate and high risk groups of patients for extra-capsular and possibly metastatic spread. There is acknowledgement that all of these scoring systems are limited and a concern that the optimal management of prostate cancer remains elusive, as 5-year biochemical failure rates for the surgical gold standard of radical prostatectomy range anywhere from 27% to 57%.

Solace is taken in the fact (based on one study) that there appears to be an 8-year gap between evidence of biochemical progression and objective metastatic disease. Currently the relative localization of the disease is based on:

- (a) digital rectal examination;
- (b) PSA value; and
- (c) histology (principally the Gleason grade)

In crude terms no radiological imaging is considered necessary in patients with a PSA less than 10, a Gleason score less than 6 and a digital rectal examination that defines a T2a or b lesion.

There are tables, linking PSA digital rectal examination and the Gleason score; the most influential being the tables of Partin who used a multi-nominal log linear

regression technique developing nomograms from a cohort of 4133 men and this is recommended as a method of counselling individual patients and with this score a probability of predicting pathological stage to within 10% was said to be 72.4%.

The question posed, therefore, is can imaging of the prostate, its immediate surroundings, including the capsule and seminal vesicles, and the local lymph nodes improve or refine staging better than those obtained by these three crude parameters?

Questions

- (1) Can T2-weighted MRI images with supplementary transverse axis scans together with coronal and sagittal scanning enhance local staging accuracy and, importantly, demonstrate extra-capsular extension?
- (2) How effective is CT scanning in distinguishing prostate cancer from benign conditions and demonstrating, reliably, extra-capsular penetration or seminal vesical invasion?
- (3) What use is CT scanning in the identification of pelvic and peri-prostatic lymphadenopathy?
- (4) What is the role of examining the bones in prostate cancer? Should radio-nuclear type bone scans be supplemented by MRI scans?
- (5) Do MRI scans have a role in identifying lymphadenopathy or is radio-immunoscintigraphy more reliable?

MR imaging of prostate cancer

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Introduction

The prostate continues to be the leading cancer site among American men with 184 500 new cases in the

USA accounting for 29% of new cancer cases in men^[1]. It has been estimated that 39 200 men in the USA died of prostate cancer in 1998. This makes prostate cancer the second cause of cancer-related death in men^[2,3].

Furthermore, the probability of developing prostate cancer from birth to death is 20%^[3]. Treatment selection is dependent on patient age and health, cancer stage and grade, morbidity and mortality of treatment, as well as patient and physician preference. The mainstay for organ-confined disease is either radical surgery or curative radiotherapy^[4,5]. This is only considered an option in the absence of seminal vesicle infiltration (SVI), extension through the prostatic capsule (extra-capsular extension, ECE) or metastatic disease. Therefore, the purpose of staging is the possible detection of extra-prostatic disease. Clinical staging by digital rectal examination (DRE) and Prostate Specific Antigen (PSA) remains as yet inaccurate. Imaging modalities such as transrectal ultrasound (TRUS) and MR imaging can be used to increase staging accuracy. This review deals with the current possibilities and limitations of MR imaging in the staging of prostate cancer.

Clinical staging methods

Accurate staging of prostate cancer is important, because treatment decisions are mainly based on the local extent of prostate cancer (ECE, SVI) and the presence of metastatic disease (lymphatic or haematogeneous). Digital rectal examination (DRE) is not an accurate staging method, as there are no gross characteristics that are reliable for distinguishing benign from malignant nodules^[6]. Furthermore, the interobserver agreement among urologists for detection of prostate cancer by DRE is only fair^[7]. Data accumulated from carefully examined prostatectomy specimens revealed that DRE underestimates the local extent of cancer in 40–60% of the cases^[8,9]. PSA is the most accurate marker to screen for prostate cancer, but has limited accuracy in staging because there is a substantial overlap in PSA-concentrations and pathological stages. Nevertheless, the combination of serum PSA concentration and other variables such as tumour grade, volume and clinical stage, significantly enhance the predictive value of serum PSA for the pathological stage^[10,11]. The probability of ECE, SVI and nodal involvement can be predicted by using the normograms of Partin^[10] that use clinical stage, Gleason score and serum prostate specific antigen (PSA).

MR imaging

MR imaging of the prostate is still in an exploratory phase and this technique is not yet advocated as a routine staging procedure. Prostate MR imaging should be performed in centres where at least 25–50 patients per year are examined and the results can be compared with histology, preferably a whole mount specimen^[12]. Currently, the major clinical indication for MR imaging is detection of ECE, SVI, nodal and bone marrow metastasis, which are contraindications for radical prostatectomy^[13]. Prostate cancer is usually visible as a low signal intensity lesion in a bright peripheral zone on

a T2-weighted image (Fig. 1). The differential diagnosis of low signal intensity areas includes cancer, haemorrhage, prostatitis, effects of hormonal or radiation treatment, benign prostate hyperplasia (BPH), scar, calcifications, smooth muscle hyperplasia and fibromuscular hyperplasia^[14]. Haemorrhage, mostly a result of biopsy, can be differentiated from cancer by evaluation of T1-weighted images. Haemorrhage is hyperintense on these images, whereas cancer has the same intensity as adjacent normal tissue. Benign prostate hyperplasia, smooth muscle hyperplasia and fibromuscular hyperplasia is located mostly in the central zone (CZ) and transitional zone (TZ), whereas cancer is primarily located in the peripheral zone (PZ). Calcifications are common in all locations of the prostate; however, these may be differentiated from cancer based on their distinct oval form. Scars are rare. Detection of cancer in the CZ and TZ is generally not possible, as this area is commonly replaced by BPH, which has an identical signal.

Staging

Several MR imaging criteria for ECE have been used. Table 1 presents commonly used criteria for ECE with its specificity and sensitivity. Most frequently used criteria are asymmetry of the neurovascular bundle, obliteration of the rectoprostatic angle and bulging of the prostate capsule (Fig. 1). SVI is detected by an abnormal asymmetric low signal intensity within the lumen on T2-weighted images (Fig. 2)^[15]. It should be noted that amyloid deposits, stones or blood could also cause low signal intensity of the seminal vesicles on T2-weighted images^[14–17].

In staging MR imaging should have a high specificity for periprostatic extension, to ensure that only few patients will be deprived of a potentially curative therapy^[18]. Sensitivity for periprostatic extension is of minor importance, because even a low sensitivity is an improvement in clinical staging^[18]. MR imaging is considered cost-effective if performed in a subgroup of patients with a prior-probability of ECE of at least 30%, that is a PSA >10 or a Gleason grade >7^[19].

The initial accuracy in 1990 for the staging of prostate cancer with MR imaging was 69%^[20]. Since then the most prominent change was the development of an endorectal coil (ERC), which resulted in faster imaging and improved spatial resolution. Accuracy for ECE with the ERC has shown a wide range between 58 and 90%^[21–24]. Several reasons for this wide range can be given. First, due to the rapidly developing MR imaging technique, different studies used different imaging protocols. Second, due to inexperience with this new method, considerable interobserver variation may be present. A third important reason is, that different studies use different criteria for ECE (Table 1) resulting in different accuracies. Although this variation remains, the use of an ERC is considered to be an improvement of the conventional MR-examination^[23–25]. Although

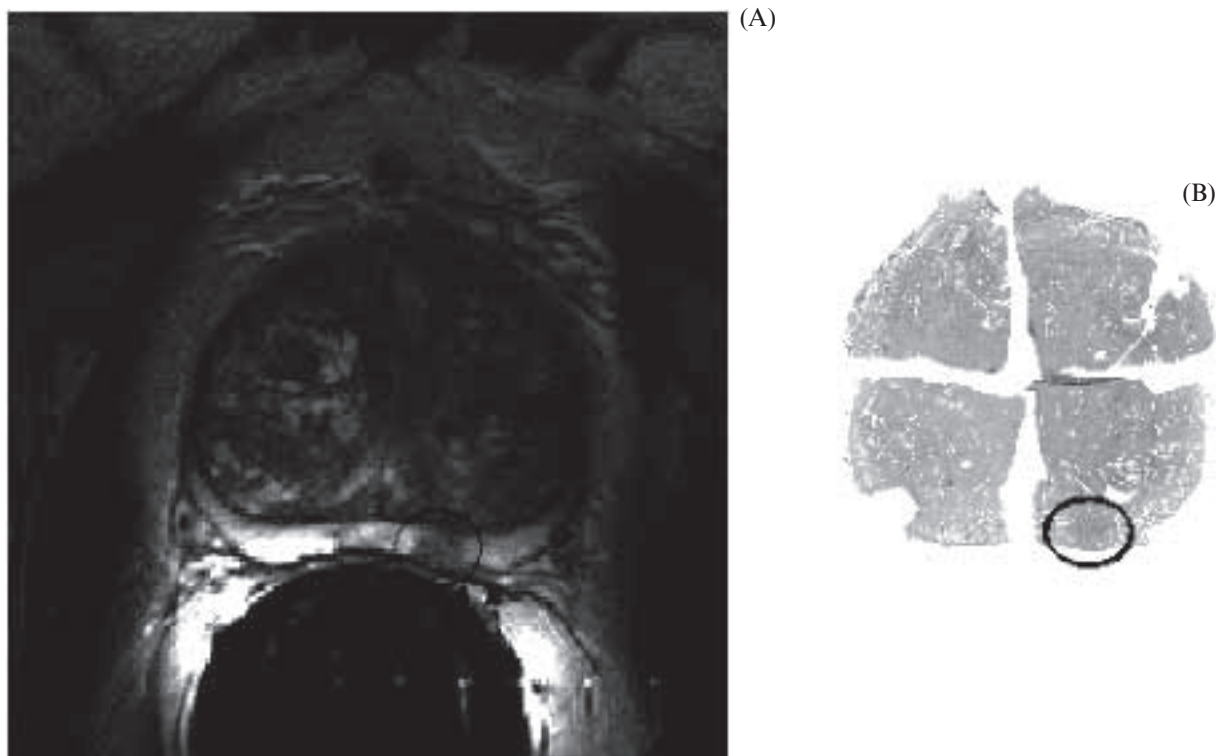


Figure 1 Patient with prostate cancer with minimal extra-capsular invasion. (A) T2-weighted axial TSE image obtained with endorectal coil (Medrad, Pittsburgh, USA). Large benign prostatic hypertrophy of central zone shows mixed signal intensity. Tumour (circle) is clearly visible as low signal lesion in high signal peripheral zone. There is minimal bulging of capsule (arrows). (B) Whole mount section revealed minimal capsular invasion at this site.

Table 1 Criteria to predict extra capsular extension of prostate cancer

Criteria for capsular penetration	Ref	Acc	Spec	Sens	PPV
Assymetry of neurovascular bundle	[61]	70%	95%	38%	—
Obliteration of rectoprostatic angle	[61]	71%	88%	50%	—
Bulge	[40]	72%	79%	46%	28%
Overall impression	[40]	71%	72%	68%	32%
Extra-capsular tumour	[40]	73%	90%	15%	34%

Acc=accuracy; Spec=specificity; Sens=sensitivity; PPV=positive predictive value; —=no data available.

major developments have changed the MR imaging technique, it still remains impossible to detect microscopic ECE^[20,22,26,27]. The detection of SVI is generally not a problem using the ERC: accuracies range between 81% and 96%^[21,23,24,26] (Fig. 2). T1- and T2-weighted images should be acquired at least 2 weeks after the prostate biopsy as haemorrhage decreases staging accuracy^[28].

Besides its role in staging, MR imaging is useful in reducing the number of false-negative prostate biopsies in patients with elevated PSA and repeated negative (TRUS guided) biopsies (Fig. 1). With MR imaging prostate cancer can be detected and then an MR-directed biopsy can be performed. Using MR imaging as a method to detect cancer lesions in a group of 36

patients with negative biopsies and elevated PSA-values, an accuracy of 78%, a positive predictive value of 74% and a negative predictive value of 84% was achieved^[29].

In summary, the role of MR imaging in local staging is not yet clearly defined, however, it is considered to be cost-effective in a select group of patients. SVI can be detected with high accuracy, which is an advantage in comparison with TRUS alone.

Metastatic disease

CT and MR imaging are reported to be the most accurate non-invasive methods of detecting pelvic lymph node metastases. Scheidler *et al.*^[30] concluded that CT and two-dimensional MR imaging perform similarly in the detection of lymph node metastasis, with a trend towards an improved accuracy of MR imaging. Therefore, both MR imaging and CT are recommended, because unlike LAG they are non-invasive. A recent study using MR imaging with a three-dimensional technique has revealed an accuracy of 90%, a positive predictive value of 94% and a negative predictive value of 89% in the detection of nodal metastasis in bladder and prostate cancer^[31]. This is clinically relevant because a high detection accuracy of nodal metastasis can facilitate the indication for (MR-guided) biopsy^[32], which in case of a positive biopsy can avoid an invasive pelvic lymph node dissection. The multiplanar reconstructions

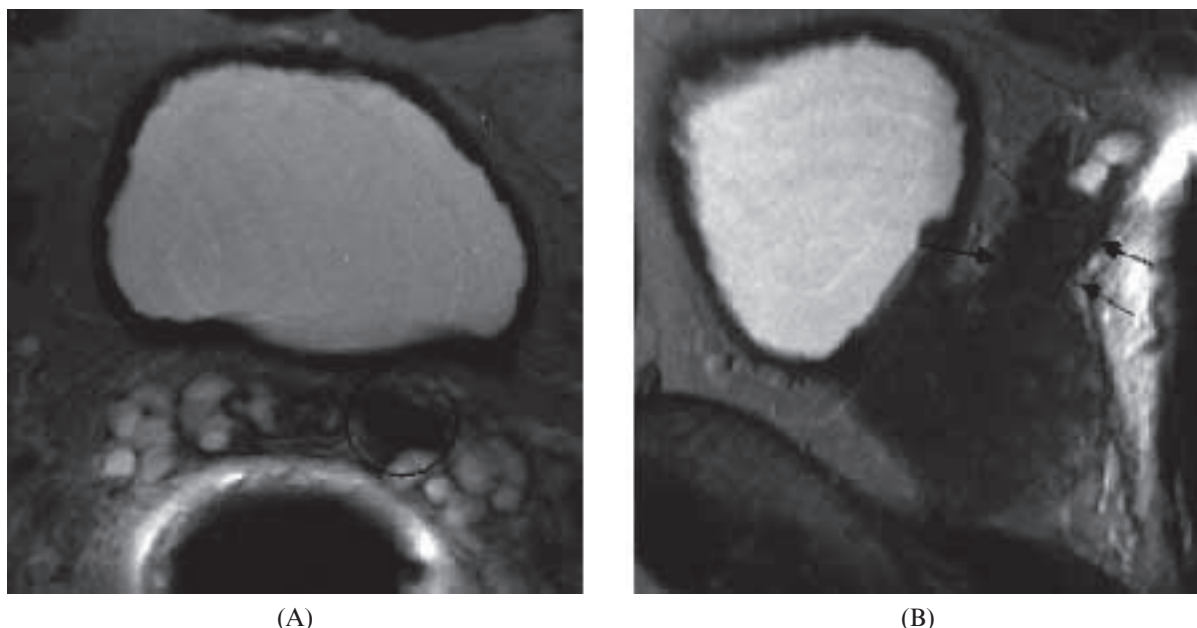


Figure 2 Patient with prostate cancer and invasion of left seminal vesicle. (A) T2-weighted axial and (B) sagittal TSE images show abnormal low signal intensity in left seminal vesicle (arrows). Confirmed by histology.

obtained with this technique allow the evaluation of not only nodal size but also nodal shape. This is important because the cut-off point between normal and metastatic nodes differs for round and oval nodes. The smallest lymph node diameter that can be detected by this method is 2 mm. Different sensitivities and specificities are acquired depending on the selection of cut-off size^[31,33,34]. In our department, we use a minimal axial diameter of 8 mm for round nodes and 10 mm for oval nodes as the upper limit of normal.

Because of the high cost CT and MR imaging in detection of nodal metastasis should only be performed in a selected group of patients with high risk for nodal metastases, which can be predicted by DRE, PSA and biopsy Gleason score^[10,31,35].

Haematogeneous metastases are most common in the axial skeleton. Currently, the mainstay for the detection of bone metastases is a radionuclide bone scan. However, it is well known that bone scans can yield false-negative findings, especially in cases of very aggressive metastases. Furthermore, the technique has a high false-positive rate mainly due to degenerative disease, healing fractures and various metabolic disorders and their complications (e.g. osteoporosis and osteomalacia). It has been demonstrated that bone scintigraphy seems to be unnecessary in the evaluation of newly diagnosed, untreated prostate cancer with no clinical signs of bone pathology and serum PSA levels of <10 ng/ml^[36]. In patients with an elevated PSA (>10 ng/ml) or with locally advanced tumours, bone scans are considered to be worthwhile for detecting both asymptomatic and symptomatic metastasis. MR imaging is more sensitive in detecting bone marrow metastases than radionuclide bone scanning^[37]. Therefore, MR imaging can be useful

in the evaluation of patients suspected of having vertebral metastases with equivocal or negative bone scans. Thanks to its high spatial resolution MR imaging may also guide needle biopsy procedures. Plain radiographs are the least sensitive in evaluating the axial skeleton for metastases. Fifty per cent of bone mineral content must be altered before there is evidence of metastases is visible.

In summary, MR imaging has a major role in detecting nodal and bone marrow metastases in patients with bladder or prostate cancer with high risk for metastatic disease.

Future developments

Fast dynamic imaging

Recent developments in MR imaging include contrast-enhanced fast dynamic MR imaging and magnetic resonance spectroscopy (MRS). Because of typical tumour enhancement characteristics, tumour tissue can be differentiated from normal tissue by fast dynamic contrast-enhanced MR imaging. On contrast-enhanced MR imaging prostate cancer shows a typical early and rapidly accelerating enhancement compared with normal tissues^[38–40] which can be used to detect the tumour, and to evaluate ECE or SVI. Other fields where dynamic MR imaging may have a potential role are therapy monitoring and the prediction of therapy success of systemic therapy of prostate cancer^[40]. Current problems with dynamic MR imaging of prostate carcinoma involve the large variation in enhancement patterns among patients with prostate carcinoma and the overlapping enhancement pattern of BPH^[41]. As the

differences in enhancement between carcinoma and normal prostate or BPH may be minimal, fast sequences should be applied. In our institution we use a time resolution of 2 s. With this resolution information seven slices can be obtained.

MRS

Image-guided proton MRS (^1H MRS) is a technique providing metabolic information about the prostate gland, which may be used for in-situ characterization, diagnosis and therapy evaluation of prostate cancer. Although the examination is comparable with MR imaging, the spatial resolution is lower (down to 0.24 cm^3 has been reported for the prostate)^[42] and the information obtained is related to metabolites rather than anatomy. It has been shown that prostate cancer is characterized by a decreased level of citrate and an increased level of (phospho)choline^[43]. Especially in the PZ, tumour tissue can be identified by an increased choline/citrate (or choline + creatine/citrate) signal-ratio^[43,44]. Correlations have been reported between metabolite ratios and the histological grade in human prostate cancers^[56]. The addition of ^1H MRS to (dynamic) MR imaging can improve tumour visualization and spatial extent^[42,46]. Potential areas of prostate cancer management that may benefit from the ^1H MRS information include targeted TRUS guided biopsies for patients with PSA levels indicative of cancer but also negative previous biopsies, therapy monitoring (watchful waiting) and guiding focal prostate cancer therapies^[47].

Nodal staging

An important limitation of CT and MR imaging in the evaluation of nodal metastasis is that both imaging methods depend on enlargement of lymph nodes as a criterion for metastasis. The problem is that metastasis may also be present in normal sized nodes, thus causing low sensitivities (75–78%)^[31,34] by not recognizing metastasis in normal-sized nodes. A solution to this problem may be the use of lymph node-specific MR-contrast agents. New MR contrast agents with ultrasmall superparamagnetic iron oxide particles are currently under investigation. In normal lymph nodes with functioning macrophages the iron oxide particles are phagocytosed and thereby decrease the signal intensity on MR imaging. Metastatic nodes, lacking macrophages, do not take up the contrast agent and hence show no change in signal on post contrast images. These agents may increase sensitivity for nodal metastasis, by detection of metastasis in normal sized nodes. Preliminary results suggest an improved accuracy in the detection of metastasis in normal size nodes using a lymph node-specific MR contrast agent^[48].

Conclusion

Accurate staging of prostate carcinoma is essential for taking treatment decisions. However, pre-operative

clinical staging is inaccurate. DRE and PSA can only provide an inexact indication of local extent. Addition of other parameters such as number of positive biopsies and biopsy grade improves clinical staging but is not accurate enough to predict tumour stage in the individual patient. Therefore, imaging modalities such as TRUS and MR imaging are needed to increase staging accuracy.

However, these imaging methods have variable accuracies. A way to increase staging accuracy and to decrease this variability may be the combination of imaging methods. For example, TRUS may be supplemented with MR imaging results. In the future, it might even be possible to fuse all imaging results: fast dynamic MR imaging, MRS, (contrast-enhanced) TRUS and colour Doppler in one image in order to achieve higher localization and staging accuracy.

Currently, the major role of MR imaging is the detection of nodal and bone marrow metastasis. In addition to detection of metastatic disease, local staging (ECE and SVI) can be done, which is at least as good and potentially superior to TRUS^[10,49]. The advantage of MR imaging is that both nodal, bone marrow and local staging can be done in one imaging session, limiting the number of examinations and cost.

In future research cost-effectiveness should be an important guideline when working with these ‘expensive’ imaging techniques. In this respect, detection of advanced disease by imaging and thereby the prevention of an unnecessary radical prostatectomy should be weighed against the cost of imaging itself and its value in assessing the stage of tumour for the individual patient.

In a recent paper Jager *et al.* determined the appropriate use of magnetic resonance (MR) imaging for pre-operative staging of prostate cancer^[51]. They performed a literature review by using the principles of evidence-based medicine and medical technology assessment. A decision analytical model was used to compare the strategy that radical prostatectomy is performed on the basis of clinical staging with the strategy that extra-capsular disease detected at MR imaging contraindicates radical prostatectomy in patients who were considered surgical candidates on the basis of clinical staging. After review of the literature, expert panel opinion did not recommend MR staging. No studies in which therapeutic efficacy was addressed were found. However, the decision analytical model indicated that the strategy including MR staging decreased costs (MR imaging, \$10 568; radical prostatectomy, \$11 669) and resulted in almost equal life expectancy (MR imaging, 12.59 years; radical prostatectomy, 12.60 years) and quality-adjusted life-years (QUALYs) (MR imaging, 12.53; radical prostatectomy, 12.52). Furthermore, results of sensitivity analyses demonstrated that the MR strategy was both more effective and less costly if the prior probability of extra-capsular disease was at least 39% when considering QUALY and 50% when considering unadjusted life expectancy.

It was concluded that it is not yet conclusively determined whether pre-operative MR staging is appropriate,

but results of decision analysis suggest that MR staging is cost-effective for men with moderate or high prior probability of extra-capsular disease.

Thus it remains very important to select appropriate patients for staging with the imaging techniques mentioned above. Finally, it should be mentioned that the role of imaging, especially MR imaging and MRS, is rapidly changing and improving and more research needs to be done to establish its definite role.

References

- [1] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics. *CA Cancer J Clin* 1998; 48: 6–29.
- [2] Imperial Cancer Research Fund. Cancer Statistics (online: <http://www.icnet.uk/research/factsheet/canstats.html>). 1995.
- [3] American Cancer Society. Cancer Facts and Figures. <http://www.cancer.org/statistics/cff98/graphicaldata.html>, 1998.
- [4] Catalona WJ. Surgical management of prostate cancer: contemporary results with anatomic radical prostatectomy. *Cancer* 1995; 75: 1903–8.
- [5] Donovan JL, Frankel SJ, Faulkner A, Selley S, Gillatt S, Hamdy FC. Dilemmas in treating early prostate cancer: the evidence and a questionnaire survey of consultant urologists in the United Kingdom. *Br Med J* 1999; 318: 299–300.
- [6] Jewett HJ. Significance of the palpable prostatic nodule. *J Am Med Assoc* 1956; 160: 838–939.
- [7] Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. *Urology* 1995; 45: 70–4.
- [8] Voges GE, McNeal JE, Redwine E, Freiha FS, Stamey TA. Morphologic analysis of surgical margins with positive findings in prostatectomy for adenocarcinoma of the prostate. *Cancer* 1992; 69: 520–6.
- [9] Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 1993; 71: 3582–93.
- [10] Partin AW, Yoo J, Ballentine Carter JY, Pearson JD, Chan DW, Epstein JI, Walsh PC. The use of prostate specific antigen, clinical stage and gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 1993; 150: 110–5.
- [11] Kleer E, Oesterling JE. PSA and staging of localized prostate cancer. *Urol Clin North Am* 1993; 20: 695–704.
- [12] Jager GJ, Barentsz JO. In: Husband J, ed. *Oncology Imaging. Prostate Cancer* 1998; 239–57.
- [13] Langlotz CP. Benefits and costs of MR imaging of prostate cancer. *MR Clin N Am* 1996; 4: 533–45.
- [14] Schiebler ML, Schnall MD, Pollack HM, Lenkinski RE, Tomaszewski JE, Wein AJ, Whittington R, Rauschnig W, Kressel HY. Current role of MR imaging in the staging of adenocarcinoma of the prostate. *Radiology* 1993; 189: 339–52.
- [15] Chernoff DM, Hricak H, Higgins CB, Hricak H. In: Hricak H, ed. *Magnetic Resonance Imaging of the Body. The Male Pelvis: Prostate and Seminal vesicles*, 3rd edition. New York: Lippincott-Raven Press, 1997: 875–900.
- [16] Ramchandani P, Schnall MD, LiVolsi VA, Tomaszewski JE, Pollack HM. Senile amyloidosis of the seminal vesicles mimicking metastatic spread of prostatic carcinoma on MR images. *Am J Radiol* 1993; 161: 99–100.
- [17] Jager G, Ruijter E, de la Rosette J, van de Kaa CA. Amyloidosis of the seminal vesicles simulating tumor invasion of prostatic carcinoma on endorectal MR images. *Eur J Radiol* 1997; 7: 552–4.
- [18] Langlotz CP, Schnall MD, Pollack H. Staging of prostatic cancer: Accuracy of MR imaging. *Radiology* 1995; 194: 645–6.
- [19] Jager GJ, Thornbury J, Barentsz JO *et al.* MR staging in prostate cancer (pc): in uence on patient outcome and effective analysis. Abstract. *RSNA* 1998; 181.
- [20] Rifkin MD, Zerhouni EA, Gatsonis CA, Quint LE, Paushter DM, Epstein JI, Hamper UM, Walsh PC, McNeil BJ. Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. *N Engl J Med* 1990; 323: 621–6.
- [21] Rørvik J, Halvorsen OJ, Albrektsen G, Ersland L, Daehlin L, Haukaas S. MR imaging with an endorectal coil for staging of clinically localised prostate cancer prior to radical prostatectomy. *Eur Radiol* 1999; 9: 29–34.
- [22] Schnall MD, Imai Y, Tomaszewski JE, Pollack HM, Lenkinski RE, Kressel HY. Prostate cancer: local staging with endorectal surface coil MR imaging. *Radiology* 1991; 178: 797–802.
- [23] Hricak H, White S, Vigneron DB, Kurhanewicz J, Kosco A, Levin D, Weiss J, Narayan P. Carcinoma of the prostate gland: MR imaging with pelvic phased-array coils versus integrated endorectal-pelvic phased-array coils. *Radiology* 1994; 193: 703–9.
- [24] Bartolozzi C, Menchi I, Lencioni R, Serni S, Lapini A, Barbanti G, Bozza A, Amorosi A, Manganelli A, Carini M. Local staging of prostate carcinoma with endorectal coil MR imaging: correlation with whole mount radical prostatectomy specimens. *Eur Radiol* 1996; 6: 339–45.
- [25] Langlotz CP, Schnall MD, Malkowicz SB, Schwartz JS. Cost-effectiveness of endorectal magnetic resonance imaging for the staging of prostate cancer. *Acad Radiol* 1996; 3: 24–7.
- [26] Chelsky MJ, Schnall MD, Seidmon EJ, Pollack HM. Use of endorectal surface coil magnetic resonance imaging for local staging of prostate cancer. *J Urol* 1993; 150: 391–5.
- [27] Outwater E, Petersen RO, Siegelman ES, Gomella LG, Chernesky CE, Mitchell DG. Prostate carcinoma: assessment of diagnostic criteria for capsular penetration on endorectal coil MR images. *Radiology* 1994; 193: 333–9.
- [28] White S, Hricak H, Forstner R, Kurhanewicz J, Vigneron DB, Zaloudek CJ, Weiss JM, Narayan P, Carroll PR. Prostate cancer: effect of postbiopsy hemorrhage on interpretation of MR images. *Radiology* 1995; 195: 385–90.
- [29] Kedar RP, Kier R, Viner N. Proceedings of the International Society of Magnetic Resonance in Medicine (poster ISMRM, Philadelphia) nr.1106, 1999.
- [30] Scheidler J, Hricak H, Yu KK, Subak L, Segal MR. Radiological Evaluation of lymph node metastases in patients with cervical cancer. *J Am Med Assoc* 1997; 278: 1096–101.
- [31] Jager GJ, Barentsz JO, Oosterhof G, Ruijs JHJ. 3D dimensional MR imaging in nodal staging of bladder and prostate cancer. *Am J Radiol* 1996; 150: 3–7.
- [32] Barentsz JO. MR-intervention in the pelvis: an overview and first experiences in MR-guided biopsy in nodal metastases in urinary bladder cancer. *Abdominal Radiol* 1997; 22: 524–30.
- [33] Vinnicombe SJ, Norman AR, Nicolson V, Husband JE. Normal pelvic lymph nodes: evaluation by CT scanning after bipedal lymphangiography. *Radiology* 1995; 194: 349–55.
- [34] Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology* 1994; 190: 315–22.
- [35] Wolf JS, Cher M, dalla'Era M, Presti JC, Hricak H, Carroll PR. The use and accuracy of cross-sectional imaging and fine needle aspiration cytology for detection of pelvic lymph node metastases before radical prostatectomy. *J Urol* 1995; 153: 993–9.
- [36] Haukaas S, Rørvik J, Halvorsen OJ, Foellings M. When is bone scintigraphy necessary in the assessment of newly diagnosed, untreated prostate cancer. *Br J Urol* 1997; 79: 770–6.
- [37] Algra PR, Bloem JL, Tissing H, Falke THM, Arndt JW, Verboom LJ. Detection of vertebral metastases: comparison between MR imaging and bone scintigraphy. *RadioGraphics* 1991; 11: 219–323.
- [38] Delorme S, Knopp MV. Non-invasive vascular imaging: assessing tumour vascularity. *Eur J Radiol* 1998; 4: 517–27.
- [39] Jager G, Ruijter E, Kaa van de C, de la Rosette J, Oosterhof G, Thornbury J, Ruijs J, Barentsz J. Dynamic Turbo-

- subtraction technique for contrast-enhanced MR images of the prostate: correlation with histopathology. *Radiology* 1997; 203: 645–52.
- [40] Brown G, Macvicar DA, Ayton V, Husband JE. The role of intravenous contrast enhancement in magnetic resonance imaging of prostatic carcinoma. *Clin Radiol* 1995; 50: 601–6.
- [41] Preziosi P, Di Giambattista G, Di Renzi P. Endorectal-coil Magnetic Resonance Imaging with dynamic subtraction technique in prostate cancer: evaluation of tumoral tissue behaviour with the time/signal intensity curve analysis (abstract). *Radiology* 1998; 209P: 259.
- [42] Kurhanewicz J, Males R, Sokolov D. Combined endorectal/phased-array MR imaging and 3-D H-MR Spectroscopic imaging for improved diagnosis of extracapsular extension in prostate cancer. Proceedings of the International Society of Magnetic Resonance in Medicine (abstract ISMRM, Philadelphia), 1998.
- [43] Heerschap A, Jager GJ, van der Graaf M, Barentsz JO, de la Rosette J, Oosterhof G, Ruijter ETG, Ruijs SHJ. In vivo proton MR spectroscopy reveals altered metabolite content in malignant prostate tissue. *Anticancer Res* 1997; 17: 1455–60.
- [44] Kurhanewicz J, Vigneron DB, Hricak H, Narayan P, Carroll P, Nelson SJ. Three-dimensional H-1 MR spectroscopic imaging of the in situ human prostate with high (0.24–0.77-cm³) spatial resolution. *Radiology* 1998; 198: 795–805.
- [45] Vigneron DB, Males R, Noworolski S. 3D MRSI of prostate cancer: correlations with histologic grade. Proceedings of the International Society of Magnetic Resonance in Medicine (abstract ISMRM, Philadelphia), 1998.
- [46] Males R, Vigneron DB, Nelson AD. Addition of MR spectroscopic imaging to mri significantly improves detection and localization of prostate cancer. Proceedings of the International Society of Magnetic Resonance in Medicine (abstract ISMRM, Philadelphia), 1998.
- [47] Weissleder R, Elizondo G, Wittenberg J, Lee AS, Josephson L, Brady TJ. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymphnodes with MR imaging. *Radiology* 1990; 175: 494–8.
- [48] Taupitz M, Barentsz JO, Tuerk I, Beyersdorff D, Fleige B, Hamm BK. MR lymphography using USIOP. Results of a clinical phase 3 trial in 31 patients with urological tumors (abstract). *Radiology* 1998; 209P: 336.
- [49] Presti JC, Hricak H, Narayan P, Shinohara K, White S, Carroll PR. Local staging of prostatic carcinoma: comparison of transrectal sonography and endorectal MR imaging. *Am J Radiol* 1996; 166: 103–8.
- [50] Yu KK, Hricak H, Alagappan R, Chernoff DM, Bacchetti P, Zaloudek CJ. Detection of extracapsular extension of prostate carcinoma with endorectal and phased-array coil MR imaging: multivariate feature analysis. *Radiology* 1997; 202: 697–702.
- [51] Jager GJ, Severens JL, Thornbury JR, de la Rosette JJMCH, Ruijs SHJ, Barentsz JO. Prostate cancer staging: should MR imaging be used: a decision analytic approach. *Radiology* 2000; 215: 445–51.

Challenges: pathologic correlation

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The pathologist's role in the management of patients suspected to have prostatic carcinoma has changed markedly in the last 20 years. Diagnostic difficulties have increased with the advent of smaller calibre biopsy guns: architectural patterns, which are key in the diagnosis of prostatic carcinoma, are not so easily assessed in these compared with the larger fragments sampled during transurethral resections. Also, as many urologists actively seek patients with organ-confined disease, an increasing proportion of biopsies is performed in younger, asymptomatic patients with low serum PSA, so that the diagnosis of carcinoma is more often made on limited foci. Finally, the potential consequences of a positive diagnosis of carcinoma are much greater than previously, as radical therapy, rather than watchful waiting, has become a more routine option.

In terms of treatment selection, the assessment of patients with prostatic carcinoma requires a multidisciplinary team approach, as no single diagnostic modality is likely to provide complete accuracy in pre-treatment staging. This is partly because of the anatomy of the prostate, which is not clearly demarcated from surrounding structures, particularly at the apex. As there is no defined capsule, it can neither be visualized clearly

by imaging nor sampled at biopsy to assess for extraglandular spread. Another limitation is that, unlike most other tumours, prostatic carcinoma does not generally produce a mass effect with centripetal spread from a single focus. In fact, examination of radical prostatectomies has shown a high incidence of multifocality, with diffuse infiltration of the stroma which separates benign glands rather than obliteration of normal anatomical structures (except in very high grade disease). As a result, it is largely impossible to identify carcinomatous foci on naked eye examination of the cut surface of the prostate, underlining the difficulties faced in imaging the gland. Another consequence of this diffuse pattern of spread is that malignant glands can benefit from the diffusion of oxygen and nutrients from the normal vasculature of the prostate, reducing the need for neo-vascularization. Although disturbances in vascular flow may still occur, the absence of consistent neo-vascularization may limit the capabilities of imaging modalities based on detecting changes in vascular density. Finally, assessment of nodal status is hampered by difficulties in pre-operative sampling, the evidence available suggesting that nodal size is a poor predictor of the presence of metastases.

Because of these limitations on direct observation and documentation of the extent of tumour spread, the predictive power of a range of pathological parameters has been tested through correlations with final staging at radical prostatectomy or with patient outcome. The earliest example of this approach was the develop-

ment of the Gleason grading system. Other parameters investigated have included the extent of carcinoma on biopsy and the presence of perineural invasion. The significance of these and other factors will be reviewed.

Planning the follow-up

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Led again by United States practice, follow-up after attempted curative treatment of prostate cancer either surgically or radiotherapeutic endeavour is by PSA alone. After much debate the definition of a raised PSA following surgery is now $>0.4 \mu\text{g/l}$, whilst that following radiotherapy is three successive rises above the upper limit of normal for the assay measuring the PSA. There is no routine utilization of any imaging modality.

Questions

- (1) Should bone scans be used on a sequential temporal basis (annually)?
- (2) Is there a role for MRI in looking at the likely sites of bone metastases?
- (3) Does CT scanning differentiate the possible recurrence locally and can it be superior to biopsy?

Prostate cancer follow-up: contribution of imaging

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The role of imaging in the follow-up of many common cancers remains controversial due to the small evidence base available to formulate guidelines. Prostate cancer has an indolent course in many men who may die with rather than due to the disease. Follow-up protocols are dictated: (1) by the need to monitor treatment response in metastatic or locally advanced disease; and (2) by the risk of current disease and the likelihood of active management of this in men without such disease. Protocols within the context of research may differ from those in routine clinical practice.

Options for follow-up include doing nothing (responding only to emergencies and other clinical problems), regular assessment (which may be performed in primary care or by clinical nurse specialists), PSA assay (usually in conjunction with this) and imaging. Their relative merits will be discussed. Follow-up imaging is

best performed with the same modality to ensure reproducibility. It is now uncommon for imaging to be the mainstay of follow-up and it is usually reserved for assessment of clinically apparent or biochemically suspected relapse.

Recurrent or progressive disease may be local, lymphatic or distant (typically skeletal metastasis). Suspected local recurrence after surgery and radiotherapy is best assessed with transrectal ultrasound which facilitates biopsy. CT is poor for assessment of small volume local recurrence, but valuable to confirm the extent of bulky disease and to plan palliative radiotherapy. It is also valuable for assessment of suspected lymphatic and visceral recurrence which may predominantly involve the retroperitoneum and upper abdomen with minimal pelvic disease following radical pelvic radiotherapy.